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Pulmonary Agenesis: A Predictor of Ipsilateral Malformations

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Pulmonary agenesis is a rare malformation that can be isolated or associated with other anomalies. We became interested in pulmonary agenesis after evaluation of a child with right pulmonary agenesis, an unlobed left lung, bilateral cleft lip and palate, maxillary and mandibular hypoplasia, bilateral microtia, bilateral radial ray hypoplasia, horseshoe kidney, and complex congenital heart disease. A review of the occurrence of pulmonary agenesis with other congenital anomalies uncovered a striking association with ipsilateral radial ray defects and/or hemifacial microsomia. The presence of bilateral facial or radial ray anomalies was indicative of bilateral pulmonary involvement. A review of the cases of pulmonary agenesis and associated anomalies at the Children's Hospital and Medical Center confirmed the association of pulmonary agenesis and ipsilateral involvement of face and/or radial ray. The association of pulmonary agenesis and ipsilateral malformations may shed light on its pathogenesis. Although the cause of these associated anomalies remains unclear, abnormalities in the development of the aortic arches during embryogenesis is an attractive hypothesis. Am. J. Med. Genet. 70:391–398, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: pulmonary agenesis; pulmonary hypoplasia; hemifacial microsomia; radial ray defects; vascular; VACTERL

INTRODUCTION

Pulmonary agenesis is an uncommon anomaly in which there is complete absence or severe hypoplasia of one or both lungs [Oyamada et al., 1953; Field, 1946; Valle, 1955]. The first reported case was by Haberlein in 1887 [Borsanyi, 1960]. Most cases reported subsequently had additional developmental defects of the skeletal, cardiovascular, gastrointestinal, and urogenital systems [Courtney, 1990]. As a result, it was suggested that pulmonary agenesis may occur as an alternate to trachio-esophageal fistula in the VACTERL sequence [Knowles et al., 1988] or as part of the Goldenhar anomaly [Downing and Kilbride, 1991]. The incidence of pulmonary agenesis associated with other structural anomalies is not known [Mardini and Nyhanm 1995]. The pathogenesis remains speculative, although vascular disruption [Van Allen, 1993; Hurwitz and Stevens, 1931] and teratogenic insult [Osborne et al., 1989] have each been considered.

We report here a review of the literature and our own clinical experience that indicates the most common overt malformations associated with pulmonary agenesis are branchial arch and/or radial ray defects. In all cases the malformations were ipsilateral to the pulmonary defects.

METHODS

Cases of pulmonary agenesis were ascertained from the literature using all case reports and literature reviews from 1937 to the present. Each case was reviewed for the presence of other malformations. Malformations of the cardiovascular system and axial skeleton were frequently associated with "isolated" pulmonary agenesis and were therefore excluded from our review. Of 269 cases ascertained, 71 had malformations other than cardiovascular and axial skeleton, including anomalies of the first and second brachial arches and/or radial ray defects (60 cases). Additional patients with pulmonary agenesis were identified through the computerized record system at Children's Hospital and Medical Center (Seattle) and eight were found with associated malformations. All cases identified from our patient population were associated with ipsilateral radial ray and/or brachial arch malforma-

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tions. The data from these eight new cases and those from the literature are reviewed here.

Clinical Reports

Patient 1. Our original patient was a male infant born after an uncomplicated pregnancy with no known exposure to drugs or alcohol in utero. Prior to his conception the parents were living 150 km from Chernobyl at the time of the accident. Multiple malformations were noted at birth. Neonatal course was complicated by respiratory distress, hypocalcemia, and pseudomonas sepsis; the patient died at age 18 days. Autopsy findings were bilateral microtia, mandibular and maxillary hypoplasia, bilateral cleft lip and palate, right pulmonary agenesis and unlobed left lung, absent right pulmonary artery, bilateral radial ray agenesis, horseshoe kidney, right thoracic hemivertebrae, atrial septal defect, patent ductus arteriosus, total anomalous pulmonary venous return draining into coronary sinus, aberrant left vertebral artery arising from the aortic arch, persistent left superior vena cava, a two vessel umbilical cord, Meckel diverticulum, and absent left lobe of the thyroid. Karyotype was 46, XY.

Patient 2. Patient 2 was a female infant born at after an uncomplicated pregnancy without known intrauterine teratogenic exposure. Findings included right microtia with preauricular tags, right mandibular and maxillary hypoplasia, right torticollis, right pulmonary agenesis, absent right pulmonary artery, retroesophageal right subclavian artery, cardiac dextroposition, and tracheal stenosis. Clinical diagnosis was VATER association and karyotype was 46, XX.

Patient 3. Patient 3 was a female infant born after an uncomplicated pregnancy without known intrauterine teratogenic exposure. Findings included left pulmonary agenesis and multiple thoracic vertebral anomalies, left chest hypoplasia, mildly hypoplastic left radius associated with absent first metacarpal, and pedunculated left thumb. Clinical diagnosis was VATER association and karyotype was 46, XX.

Patient 4. Patient 4 was a female infant born after an uncomplicated pregnancy with no known intrauterine teratogenic exposure. Mother was taking Clomid and Premarin to induce ovulation and conception. Neonatal course was complicated by tachypnia and cyanosis. Left pulmonary agenesis was diagnosed subsequently. Additional findings included left pulmonary agenesis, left auricular pits, a left preauricular pit, and thirteen left ribs. Clinical diagnosis was VATER association.

Patient 5. Patient 5 was a female infant born after an uncomplicated pregnancy with no known intrauterine teratogenic exposure. Prenatal history was significant for 1 week of vaginal bleeding at 9 weeks of gestation. Neonatal course was complicated by respiratory distress and cyanosis. Right pulmonary agenesis was subsequently diagnosed. Following progressive respiratory failure with unsuccessful resuscitation, the infant expired on the first day of life. Autopsy findings were right pulmonary agenesis, incomplete lobation of left lung, tracheal stenosis, pulmonary artery sling, anomalous venous return, polysplenia, hypoplastic left umbilical artery, preaxial polydactaly of left thumb, and aplasia of urachus. Clinical diagnosis was VATER association and karyotype was 46, XX.

Patient 6. Patient 6 was a male infant born after an uncomplicated pregnancy without known intrauterine teratogenic exposure. At birth, multiple congenital anomalies were noted, including a cleft palate, severe microtia, hypoplasia of the left maxilla and mandible, single umbilical artery, and an imperforate anus. Neonatal course was complicated by respiratory distress and failure to thrive and subsequently absence of the left lung and multiple rib and vertebral anomalies were noted. At age 5 months the infant died following respiratory failure. At autopsy findings included agenesis of left lung, left microtia and mandible hypoplasia, cleft palate, multiple rib and vertebral anomalies, hypoplasia of left chest, single umbilical artery, and imperforate anus. Clinical diagnosis was VATER association. Karyotype not performed.

Patient 7. Patient 7 was a male infant born after an uncomplicated pregnancy without known intrauterine teratogenic exposure. Neonatal course was complicated by cyanosis and respiratory distress and subsequently complex congenital heart disease and right pulmonary agenesis were diagnosed. Bilateral radial ray hypoplasia was noted at birth. Elective extubation was performed and the infant died at 22 days of life. At autopsy, findings included agenesis of right lung, an unlobed left lung, AV canal, common atria, single ventricle, coarctation of the aorta, patent ductus arteriosa, absent right pulmonary vasculature, high arched palate, broad frenulum, bilateral radial hypoplasia, and digitalized thumbs. No syndromic diagnosis was made. Karyotype not performed.

Patient 8. Patient 8 was a male infant born after an uncomplicated pregnancy without known teratogenic exposure. At birth, multiple congenital anomalies were noted including T12-L3 menigomyelocoel, right oblique facial cleft with absence of the right orbit and nasal ala, right cleft of the primary and secondary palate, right external auditory canal atresia, club feet, and bilateral single palmar creases. Cranial ultrasound detected hydrocephalus and agenesis of corpus callosum. Hypoplastic right lung was noted on routine chest radiograph and bronchoscopy performed to investigate cause of stridor identified hypoplasia of right mainstem bronchus and aplasia of right upper lobe bronchus. No syndromic diagnosis was made. Karyotype was 46, XY.

RESULTS

Seventy-one cases of pulmonary agenesis associated with other malformations were reviewed. Sixty cases were associated with malformations of the derivatives of the first and second branchial arches and/or radial ray defects. Data from these 60 cases and 8 new cases from our institution are reviewed here.

Right Pulmonary Agenesis

Of these cases, 49% had agenesis of the right lung, 41% had left agenesis of the left lung, and 10% had bilateral pulmonary dysgenesis. Of those with right pulmonary agenesis, 39% had ipsilateral hemifacial microsomia, 49% had ipsilateral radial ray defects, and 12% had both hemifacial microsomia and radial ray defects. Other associated anomalies were found (i.e., cardiac and vertebral defects) and are noted in Table I.

Left Pulmonary Agenesis

Of these cases, 41% had left pulmonary agenesis. Of those, 39% had ipsilateral hemifacial microsomia, 50% had ipsilateral radial ray defects, and 11% had both hemifacial microsomia and radial ray defects. Other associated anomalies are noted in Table II.

Bilateral Pulmonary Dysgenesis

Of these cases, 11% identified had unilateral pulmonary agenesis with the remaining lung lacking normal lobation; 57% of those cases were associated with hemifacial microsomia, 29% with radial ray defects, and 14% were associated with hemifacial microsomia and radial ray defects (Table III).

Of the 79 cases of pulmonary agenesis associated with other malformations reviewed here, 51% were associated with ipsilateral radial ray hypoplasia, 42% with ipsilateral malformations of the derivatives of the first and second branchial arches, and 13.9% with structural malformations other than radial ray or branchial arch (excluding the common association of pulmonary agenesis and vertebral and cardiac malformations). In the population without malformations of the radial ray or branchial arch derivatives, imperforate anus and cardiac malformations are present in over 50% (Fig.1).

DISCUSSION

Pulmonary agenesis is an uncommon malformation, which has been described as an isolated lesion or associated with other anomalies. In 1955 Riordan suggested the association of congenital absence of the radius with aplasia or collapse of the lung on the affected side. Since then a number of reviews and case reports of agenesis of the lung and associated anomalies have been published. Anomalies associated with pulmonary agenesis include those of the skeletal, cardiac, gastrointestinal, urogenital, and upper respiratory systems as well as limb and facial defects [Devi and Moore, 1996; Opitz and Faith, 1969; Courtney, 1990; Novak, 1981]. As a result of these reported cases, pulmonary agenesis has been considered as part of the VACTERL sequence [Knowles, 1988] or Goldenhar syndrome [Opitz, 1964; Bowen and Parry, 1980]. The 68 cases of pulmonary agenesis associated with ipsilateral facial and/or radial ray defects described in our review may indeed represent a subset of VACTERL or Goldenhar syndrome. However, we have found that malformations of first and second arch derivatives and/or the radial ray defects are the most common overt malformations associated with pulmonary hypoplasia (occurring in 82% of the 79 reported cases of pulmonary agenesis associated with other malformations). Cases without malformations of the face and/or radial ray appear to fit the clinical picture of the VATERL association and have a much higher incidence of imperforate anus and cardiac malformations (Fig. 1).

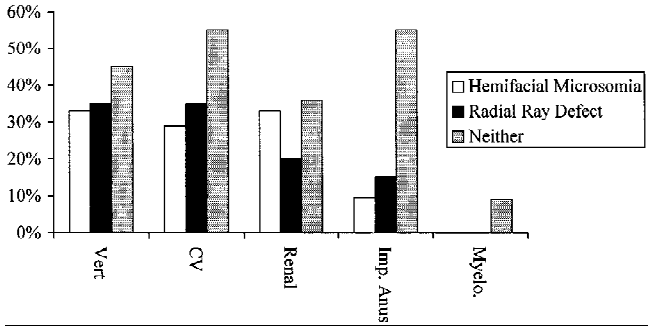

Fig. 1. Malformations associated with cases of pulmonary agenesis in the absence of radial ray and facial anomalies. Vert, vertebral anomalies; CV, cardiovascular malformations; Myelo., myelomeningocele.

In all cases, ours and those reported in the literature, face and radial ray malformations were ipsilateral to the pulmonary malformations. In cases of bilateral pulmonary involvement, the radial ray and/or branchial arch malformation was occasionally on the side of the less involved lung; however, bilateral facial and/or radial ray anomalies appeared to be indicative of bilateral pulmonary involvement. The pathogenesis of isolated pulmonary agenesis, oculo-auriculo-vertebral spectrum, and radial ray anomalies remains obscure [Opitz et al., 1989]. A vascular disruption sequence was suggested for each of these anomalies when they occur in isolation [Hurwitz and Stevens, 1937; Van Allen, 1992]. Our review of the association of pulmonary agenesis and ipsilateral radial ray hypoplasia and/or hemifacial microsomia occurring as a distinct association may shed light on the pathogenesis of each of these isolated malformations. We suggest that an alteration or disruption in dorsal aortic arch blood flow in the fourth week of gestation could selectively interfere with the development of the lung, limb, and derivatives of the first and second branchial arches explaining the ipsilateral nature of the described malformations.

During the fourth week of gestation there is simultaneous growth of the primary lung bud, emigration of cephalic neural crest to populate the first and second branchial arches, and dramatic outgrowth of the forelimb bud. Each of these tissues are supplied with blood flow from either the sixth aortic arch (lung bud), first and second aortic arches (maxillary and stapedial arteries, supplying the first and second branchial arches, respectively), and fourth aortic arch or seventh intersegmental artery (supplying the right and left limb bud, respectively). Each of these vascular supplies are present during the period in which we would expect the reported malformations to occur. The striking ipsilateral nature of the cases from our institution and the literature would seem to support a vascular etiology due to the nature of the paired dorsal aortic arches at this stage of development. Further support of this theory is that two of our eight new cases demonstrated

TABLE I. Right Agenesis*

Case	Pulmonary dysgenesis	Maxillary hypoplasia	Mandibular hypoplasia	Ear anomalies	Radial ray defects	Vertebral anomalies	Renal anomalies	Cardio-vascular defects	Other
2	Right	Right	Right	Right				Absent R subclavian	
8	Right	Right	Right	Right			Right		Myelo-menigocele
Jones [1961]	Right			Bilateral			Horseshoe	ASD	
Smith et al. [1958]	Right			Bilateral	Right				
Booth et al. [1967]	Right		+	Right	Right				
Booth et al. [1967]	Right		Right						
Matz et al. [1968]	Right			+		+	Right		
Yount et al. [1948]	Right			Right					Twin w/R pulm agenesis
Levi et al. [1948]	Right	Right	Right						
Werner et al. [1960]	Right			Right					
Bowen et al. [1980]	Right	Right		Bilat. R>L		+			
Kenawi et al. [1976]	Right		Right	Bilat.			Horseshoe		
Pierpont et al. [1982]	Right		Right	Right	Right	+		VSD, coarct, TOGV	
Pierpont et al. [1982]	Right	Right	+	Bilateral		+			
Hess et al. [1979]	Right			Right				ASD	
Morand et al. [1978]	Right			Right				TOGV	
Topper et al. [1990]	Right		Right	Right	Right	+	Right		
Mardini et al. [1985]	Right				Right	+		ASD	
Mardini et al. [1985]	Right				Right			ASD	
Borsanyi et al. [1960]	Right				Right				
Henchman et al. [1964]	Right				Right		Right	+	Imperforate anus
Jones et al. [1961]	Right				Right		Right		Imperforate anus
Riordan et al. [1955]	Right				Right	+	Right		
Riordan et al. [1955]	Right				Right	+			

(*Continued*)

TABLE I. (*Continued*)

Case	Pulmonary dysgenesis	Maxillary hypoplasia	Mandibular hypoplasia	Ear anomalies	Radial ray defects	Vertebral anomalies	Renal anomalies	Cardio-vascular defects	Other
Riordan et al. [1955]	Right				Right	+			
Gilley et al. [1928]	Right				Right				
Maltz et al. [1968]	Right				Right			+	
Saxl et al. [1940]	Right				Right				
Frias et al. [1974]	Right				Right	+			Absent R pectoral muscle
Osborne et al. [1989]	Right	+			Right	+			
Osborne et al. [1989]	Right				Right	+			
Osborne et al. [1989]	Right				Right	+			
Knowles et al. [1988]	Right				Right				

*ASD, atrial septal defect; VSD, ventricular septal defect; TOGV, transposition of the great vessels; PFO, patent foramen ovale; PDA, patent ductus arteriosus; RVH, right ventricular hyperplasia; SVC, superior vena cava; TAPVR, total anomalous pulmonary venous return. + indicates that the anomaly was reported but not described in detail.

aortic arch malformations (case 2 and 5). Retroesophageal right subclavian and absent left subclavian artery both represent anomalous development of the branches of the paired aortic arches.

An alternative hypothesis for the association of pulmonary, radial ray, and branchial arch malformations could be generated based on the blastogenic model of embryonic development. During the period of blastogenesis (week 1 through week 4 of human development), there is transformation of a bilaterally symmetric unilaminar embryo to an laterally asymmetric embryo containing all the primordia of organs and skeletal structures of the adult form [Opitz, 1993]. During this critical phase of development the specification of neural crest, limb, and lung formation is determined. Although the inductive mechanisms responsible for this pattern formation remain incomplete, key regulatory molecules are beginning to emerge through modern molecular developmental biology. Several growth factors including members of the Hedgehog gene family (Sonic, Desert, and Indian), bone morphogenic proteins; transcription factors: Sna (Snail zinc finger protein), HMG box factors (TCF-1 and LEF-1); protooncogenes (ets-2); and matrix molecules (cadherin 11) have expression patterns during vertebrate development that might explain the constellation of malformations we have described [Bitgood and McMahon, 1995; Smith et al., 1992; Oosterwegel et al., 1993; Maroulakou et al., 1994; Simonneau et al, 1995]. Although the expression of these genes is not restricted to the derivatives of the branchial arches, lung primordium, and limb, their colocalization in these regions may give insight into the pathogenesis of the associated malformations we have described. If, in fact, the ipsilateral nature of the malformations of this association is due to abnormal development of the of the aortic arches, this may represent a secondary event following abnormal patterning during blastogenesis. We would expect abnormalities in the patterning of the limb, lung, and face during the period of blastogenesis is likely due to multiple epigenetic and environmental factors.

Although abnormal development of the aortic arches remains an attractive hypothesis for the etiology of these ipsilateral pulmonary, facial, and limb anomalies many questions remain.

1) Explanations are needed for why the malformations are not always ipsilateral, 2) what is the inciting event that leads to alteration in aortic arch flow, and 3) why those individuals with bilateral pulmonary involvement can have limb and/or face malformations more severe on the side contralateral to the more severe lung involvement? Each of these questions can be explained by the involvement of vascular growth factors necessary for normal vessel development. If soluble growth factors are necessary for the development of the aortic arches one would expect that local deficiency would result in ipsilateral malformations more commonly that contralateral. Endothelin-1 (ET-1) is a peptide implicated in widespread functions during development. In situ hybridization has localized mRNA expression of the pre-pro-peptide in the epithelium of the developing branchial arches and the endo-

TABLE II. Left Agenesis*

Case	Pulmonary dysgenesis	Maxillary hypoplasia	Mandibular hypoplasia	Ear anomalies	Radial ray defects	Vertebral anomalies	Renal anomalies	Cardio-vascular defects	Other
3	Left				Left	+	+		
4	Left			Left		+			
6	Left	Left	Left	Left					
Mardini et al. [1985]	Left		Left	Left		+			
Smith et al. [1958]	Left	+	+	Bilateral			Left	VSD	
Booth et al. [1967]	Left		+	Left	Left	+			
Ferguson et al. [1944]	Left			Left					
Foquet et al. [1951]	Left	Left	Left						
Bariety et al. [1955]	Left	Left	Left						
Wilson et al. [1958]	Left	Left	Left	Left		+			
Pierpont et al. [1982]	Left			Left	Left	+			
Gorlin et al. [1963]	Left			Bilateral	Left	+	Bilateral		
Mardini et al. [1985]	Left					+	Left	Ventricular aneurysm	
Smith et al. [1958]	Left				Bilateral		Left	ASD, VSD	Imperforate anus
Booth et al. [1967]	Left				Left	+			
Ferguson et al. [1944]	Left				Left				
Altman et al. [1929]	Left				Left	Bilateral		PFO, PDA	
Forminje et al. [1938]	Left				Left				
Saxl et al. [1940]	Left				Left				
Paul et al. [1928]	Left				Left				
Osborne et al. [1989]	Left				Left	+			
Osborne et al. [1989]	Left				Left	+		Pulmonary stenosis	
Choisser et al. [1939]	Left		Left					RVH	
Dowing et al. [1991]	Left		Left	Left		+		VSD	Agenesis of corpus callous

(*Continued*)

TABLE II. (*Continued*)

Case	Pulmonary dysgenesis	Maxillary hypoplasia	Mandibular hypoplasia	Ear anomalies	Radial ray defects	Vertebral anomalies	Renal anomalies	Cardio-vascular defects	Other
Knowles et al. [1988]	Left				Left	+			Absent L pectoral muscle
Knowles et al. [1988]	Left				Bilateral	+	Horseshoe	ASD, VSD	Imperforate anus
Knowles et al. [1988]	Left				Left	+	Horseshoe	ASD, VSD	Imperforate anus
Davis et al. [1996]	Left				Left	+	L agenesis		Hypoplastic scrotum

*See Table I footnote for explanation of abbreviations.

thelium of the dorsal aortae and developing lung [Chan et al., 1995]. If ET-1 or a similar molecule has a "paracrine" function during vessel formation or maintenance, regional reduction of protein could selectively effect ipsilateral development of a variety of structures. The highest level of mRNA localization of ET-1 is in the developing lung. If ET-1 is necessary for regional vessel growth and the lung is the primary source of functional protein, pulmonary agenesis could lead to ipsilateral vessel maldevelopment and subsequent structural malformations. The apparent paradoxical association in some individuals of more severe lung involvement on the side contralateral to severe facial or limb anomalies can also be explained by this general model. Although the lack of lung/vessel secreted growth factors would be most likely to cause ipsilateral malformations, the very nature of secretion of a factor into a vascular system would allow for more varied downstream effects.

There are two areas of possible ascertainment bias in our review. First, we have chosen to exclude patients with pulmonary agenesis and only cardiac or vertebral malformations. Second, it is possible that there has been a disproportionate reporting of ipsilateral malformations in the literature due to there striking clinical appearance. Our purpose was to attempt to define a population of patients with similar structural malformations such that a common etiology might be found. A focused description of a group of patients with distinct malformations may be helpful in determining a teratologic or molecular cause. As the patients from the literature were ascertained by reviewing the literature of pulmonary agenesis, we do not feel the ipsilateral phenomenon of other malformations represents a selection bias.

In summary, we have found that all cases of pulmonary hypoplasia/agenesis associated with radial ray defects or hemifacial microsomia have ipsilateral malformations. The ipsilateral nature of these malformations suggests an abnormality in aortic arch development or blood flow may be the inciting developmental event.

TABLE III. Bilateral Dysgenesis*

Case	Pulmonary dysgenesis	Maxillary hypoplasia	Mandibular hypoplasia	Ear anomalies	Radial ray defects	Vertebral anomalies	Renal anomalies	Cardiac defects	Other
1	R agenesis, L unlobed	Bilateral	Bilateral	Bilateral	Bilateral	Right	Horseshoe	ASD, TAPVR	
5	R agenesis, L incomplete lobation				Left			Absent L subclavian artery with pulmonary artery sling	Polysplenia and aplasia of urachus
7	R agenesis, L unlobed				Bilateral			Common antrium, VSD	2 SVC
Gross et al. [1905]	L agenesis, R unlobed	Left	Left	Bilateral			Right		Imperforate anus
Maltz et al. [1968]	R agenesis, L unlobed			Left					
Debuse et al. [1973]	Bilateral agenesis		Bilateral				Left	Pulmonary artery anomalie	Imperforate anus
Opitz et al. [1969]	Bilateral unlobed, R hypoplastic		Left	Bilateral				Coartation of the aorta	

*See Table I footnote for explanation of abbreviations.

Although more research is necessary to determine the pathogenesis, due to the ipsilateral pattern of malformations, we suggest that this constellation of developmental defects should be considered a distinct malformation complex which may be caused by relative deficiency of a diffusible vessel-derived growth factor.

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